(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 October 2002 (17.10.2002)

PCT

(10) International Publication Number
WO 02/081504 A3

(51) International Patent Classification[7]: C07K 14/16, 16/10, G01N 33/68, A61K 38/16, A61P 31/18

(21) International Application Number: PCT/US02/11218

(22) International Filing Date: 8 April 2002 (08.04.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/282,270 6 April 2001 (06.04.2001) US

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(81) Designated States *(national)*: AU, CA, JP.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:
— *with international search report*

(88) Date of publication of the international search report:
10 April 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/081504 A3

(54) Title: MULTIMERIZATION OF HIV-1 VIF PROTEIN AS A THERAPEUTIC TARGET

(57) Abstract: One approach to treating individuals infected with HIV-1 is to administer to such individuals compounds that directly interfere with and intervene in the machinery by which HIV-1 replicates itself within human cells. Although the specific role of HIV-1 viral protein Vif in the viral life cycle is not known, the *Vif* gene is essential for the pathogenic replication of lentiviruses*in vivo*. The present invention relates to a method for treating an individual exposed to or infected with HIV-1. Individuals identified as being exposed to or infected by HIV-1 are administered a therapeutically effective amount of one or more compounds that inhibit or prevent replication of said HIV-1 by interfering with the replicative or other essential functions of HIV-1 viral protein Vi, by interactively blocking the multimerization domain of Vif, thereby preventing multimerization of Vif protein, which is important for Vif function in the lentivirus life cycle. In preferred embodiments, the compound or compounds that interactively block the multimerization domain of Vif are Vif antagonists. Pharmaceutical compositions comprising these compounds are also disclosed.

INTERNATIONAL SEARCH REPORT

Int ional Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/16 C07K16/10 G01N33/68 A61K38/16 A61P31/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07K G01N A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, SEQUENCE SEARCH, BIOSIS, EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 330 359 A (BIO-RAD LABORATORIES, INC.) 30 August 1989 (1989-08-30) the entire document, in particular pages 3 and 8, table 1 and claims 1-19	1-5, 7-10,12, 13
X	EP 0 959 136 A (INTROGENE B.V.) 24 November 1999 (1999-11-24) SEQ ID NO 3; page 2; claim 11	1-7

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2002	30/12/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Schmidt, H

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHOPPIN J ET AL.: "Analysis of Physical Interactions between Peptides and HLA Molecules and Application to the Detection of Human Immunodeficiency Virus 1 Antigenic Peptides" JOURNAL OF EXPERIMENTAL MEDICINE, vol. 172, September 1990 (1990-09), pages 889-899, XP000603680 table 1 ---	1-4
X	FRIEDLER A ET AL.: "Peptides Derived from HIV-1 Vif: A Non-substrate Based Novel Type of HIV-1 Protease Inhibitors" JOURNAL OF MOLECULAR BIOLOGY, vol. 287, 1999, pages 93-101, XP002219618 figure 1 ---	1-4
X	JIN X ET AL.: "Identification of Subdominant Cytotoxic T Lymphocyte Epitopes Encoded by Autologous HIV Type 1 Sequences, Using Dendritic Cell Stimulation and Computer-Driven Algorithm" AIDS RESEARCH AND HUMAN RETROVIRUSES, vol. 16, no. 1, January 2000 (2000-01), pages 67-76, XP002219619 table 1 ---	1-4
X	YANG S ET AL.: "The Multimerization of Human Immunodeficiency Virus Type I Vif Protein" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 276, no. 7, 8 November 2000 (2000-11-08), pages 4889-4893, XP002219620 the whole document -----	11

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INTERNATIONAL SEARCH REPORT

rnational application No.
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Box I Observati ns where certain claims were found unsearchable (Continuation of item 1 f first sh et)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12 and 13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-4, 7-10, 12 and 13 (all partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 11 (completely) and 1-5,7-10,12,13 (partially)

   peptide having SEQ ID NO 5, its compositions, antibodies and methods and method of identifying a Vif antagonist

2. Claims: 1-5,7-10,12 and 13 (all partially)

   peptide having SEQ ID NO 6, its compositions, antibodies and methods

3. Claims: 1-5,7-10,12 and 13 (all partially)

   peptide having SEQ ID NO 7, its compositions, antibodies and methods

4. Claims: 1-5,7-10,12 and 13 (all partially)

   peptide having SEQ ID NO 8, its compositions, antibodies and methods

5. Claims: 1-10,12 and 13 (all partially)

   peptide having SEQ ID NO 9, its compositions, antibodies and methods

6. Claims: 1-5,7-10,12 and 13 (all partially)

   peptide having SEQ ID NO 10, its compositions, antibodies and methods

7. Claims: 1-10,12 and 13 (all partially)

   peptide having SEQ ID NO 11, its compositions, antibodies and methods

8. Claims: 1-5,7-10,12 and 13 (all partially)

   peptide having SEQ ID NO 12, its compositions, antibodies and methods

9. Claims: 1-10,12 and 13 (all partially)

   peptide having SEQ ID NO 13, its compositions, antibodies and methods

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

10. Claims: 1-5,7-10,12 and 13 (all partially)

peptide having SEQ ID NO 14, its compositions, antibodies and methods

11. Claims: 1-5,7-10,12 and 13 (all partially)

peptide having SEQ ID NO 15, its compositions, antibodies and methods

12. Claims: 1-5,7-10,12 and 13 (all partially)

peptide having SEQ ID NO 16, its compositions, antibodies and methods

13. Claims: 1-5,7-10,12 and 13 (all partially)

peptide having SEQ ID NO 17, its compositions, antibodies and methods

14. Claims: 1-5,7-10,12 and 13 (all partially)

peptide having SEQ ID NO 18, its compositions, antibodies and methods

15. Claims: 1-5,7-10,12 and 13 (all partially)

peptide having SEQ ID NO 19, its compositions, antibodies and methods

16. Claims: 1-5,7-10,12 and 13 (all partially)

peptide having SEQ ID NO 20, its compositions, antibodies and methods

17. Claims: 1-5,7-10,12 and 13 (all partially)

peptide having SEQ ID NO 21, its compositions, antibodies and methods

18. Claims: 1-5,7-10,12 and 13 (all partially)

peptide having SEQ ID NO 22, its compositions, antibodies and methods

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

19. Claims: 1-5,7-10,12 and 13 (all partially)

peptide having SEQ ID NO 23, its compositions, antibodies and methods

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4, 7-10, 12 and 13 (all partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty, e.g. 19653 documents disclosing a peptide comprising a PXP motif and having between 5 to 20 amino acid residues. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

Furthermore, present claims 1-4,7-10, 12 and 13 relate to a compound defined by reference to a desirable characteristic or property, namely its ability to bind to the multimerization domain within a Vif protein. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Moreover, present claims 8-10 relate to an extremely large number of possible antibodies. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the antibodies claimed.
It is unclear in the sense of Article 6 PCT what is meant by a derivative of a single-chain antibody (see claims 8 and 10). This expression may comprise a wide range of compounds and are therefore speculative, embracing a great variety of possibilities not yet explored by the applicant, the effect of which cannot be expected by the skilled person using the teaching disclosed in the current application and his technical knowledge to reproduce without undue burden all the possibilities which are actually claimed.

For these reasons, a meaningful search over the whole breadth of the claims is impossible.
Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to peptides having SEQ ID NOs 5-23, pharmaceutical compositions containing the same, antibodies thereof and their methods.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/11218

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 0330359	A	30-08-1989	AU	3076189 A	31-08-1989
			EP	0330359 A2	30-08-1989
			JP	1308299 A	12-12-1989
EP 0959136	A	24-11-1999	EP	0959136 A1	24-11-1999
			AU	4064099 A	06-12-1999
			CA	2329270 A1	25-11-1999
			EP	0960942 A2	01-12-1999
			WO	9960147 A2	25-11-1999